Artificial Intelligence Based Insulin Sensitivity Prediction for Personalized Glycaemic Control in Intensive Care

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Abstract: **Stress-induced hyperglycaemia is a frequent complication in intensive therapy that can be safely and efficiently treated using the recently developed model-based tight glycemic control (TGC) protocols. The most widely applied TGC protocol is the STAR (Stochastic-TARgeted) protocol, which uses the patient's insulin sensitivity (SI) to assess the patient's state. The patient-specific metabolic variability is managed by the so-called stochastic model allowing the prediction of the 90% confidence interval of the patients' future SI value. In this paper, a deep neural network based method is suggested to implement the patient state prediction. The deep neural network is trained by using three years of STAR treatment data. The method is validated by comparing the prediction statistics with the reference data set. The prediction accuracy was also compared with the stochastic model currently used in the clinical practice. The presented results proved the applicability of the neural network based methods for the patient state prediction in the model-based clinical treatment. Results suggest that the method's prediction accuracy was the same or better than the currently used stochastic model. These results are the initial successful step in the proposed methods' validation procedure and will be further validated by in-silico simulation trials.**

Introduction

Stress-induced hyperglycaemia is a frequent complication in intensive therapy [1,2]. Forcing the blood glucose (BG) level of these hyperglycaemic patients into the normoglycaemic range shows definite clinical benefits. This therapy is called tight glycemic control (TGC), which includes insulin therapy and occasionally moderation of the nutrition intake of the patient.

The recently developed model-based TGC protocols successfully implement safe and efficient patient treatment [3]. The STAR (Stochastic-TARgeted) TGC protocol is the most widely applied among them; it is used in four different countries [4]. STAR uses the patient-specific insulin

sensitivity (SI) as a key parameter [5] to define the patient's state. SI describes the patient metabolic response to insulin. SI is identified from the clinical treatment data during the treatment of the patients.

In the so-called 2D stochastic model of insulin sensitivity, the conditional density function defining the conditional probability distribution of SI(t+1) for a given SI(t) is used to determine the 90% confidence interval of SI in the future [6]. This is a crucial step in the STAR protocol to handle the patient's state's future variability directly. The 2D stochastic model was created based on the treatment data of the SPRINT protocol using kernel fitting.

In this paper, an Artificial Intelligence (AI), especially the Neural Network (NN) based method [7] is presented to create an alternative model for the STAR protocol.

The potential benefits of using an NN based solution are the flexibility of the method to involve additional patient parameters into the prediction and the opportunity to incrementally modify the stochastic model based on recent patient treatments.

The benefits of involving additional patient parameters in the SI prediction have already been shown by developing the so-called 3D stochastic model [8]. The AI-based method allows to easily apply different patient parameters, like BG measurements, into the prediction method.

Methods and Data

SI Prediction Problem

During the patient's STAR treatment, the SI value, representing the patient's actual state, is identified every hour. The stepwise time function is used to create the {;} data pairs. The prediction from was achieved by using a stochastic model. The stochastic model will be defined in the current research by a Neural Network-based Artificial Intelligence method. Thus, our problem is to define the function giving for given based on this data set.

Deep neural networks as supervised machine learning will be suggested to learn the mapping between the input and the output values. The NN based classification models are used to predict the class of a given input, and the NN based regression models are used to predict continuous output values, often the most likely value of a distribution.

The core of the problem is that the STAR protocol needs an interval instead of a concrete SI(t+1) value. Therefore a classic regression method

hardly usable to predict the two limits of the interval due to the lack of direct training data. Instead, a classification model was created and used with additional post-process steps to calculate and learn the conditional distribution of SI(t+1).

Patient Selection and SI Data Set Used

All the patients treated by STAR between June 2016 and August 2019 in Christchurch Hospital, New Zealand, were included in the study cohort. The following exclusion criteria were applied:

- patients treated less than 10 hours by STAR;
- sections of treatments where the higher border of the BG target band was above 9 mmol/L;
- sections of treatments where the lower border of the BG target band was above 6 mmol/L.

Data points used for the creation of the prediction models are created for each real BG measurements. The actual and values are identified based on the treatment data. The total number of data points was 62 433.

SI Prediction Based on Deep Neural Network

To apply the classification deep neural network (CDN) for the prediction of the distribution based on , the codomain of was divided into 128 equal-size intervals. Each interval was associated with one output class. The input of the CDN is the value. The output layer of the CDN consists of 128 nodes related to the classes defined above. The CDN nodes will define for each output class the probability that the SI domain associated with the given class includes the predicted value. Thus, the output can be considered as the discrete distribution of .

A classical multi-class classification architecture was used. The activation functions in the hidden dense layers were tangent-hyperbolic functions. In the output layer the softmax function was used. The loss function was the categorical crossentropy function.

The training data set contains SI(t) pairs and the one-hot encoded class number of .

The deep neural network used for SI prediction was implemented in Python using TensorFlow and Keras. 80% of the input data set was used for training. The training consisted of 20 epochs.

The final result of the SI prediction is calculated by fitting a Gaussian distribution to the output of the deep neural network, which is considered in this case as a histogram. The STAR protocol needs a 90% confidence

interval over the SI(t+1) conditional distribution. Therefore the 5th and 95th percentile value of the fitted Gaussian distribution was used. 90% of the possible SI values are between those two border values, and the width of the interval is minimal. Figure 1 shows a prediction output example.

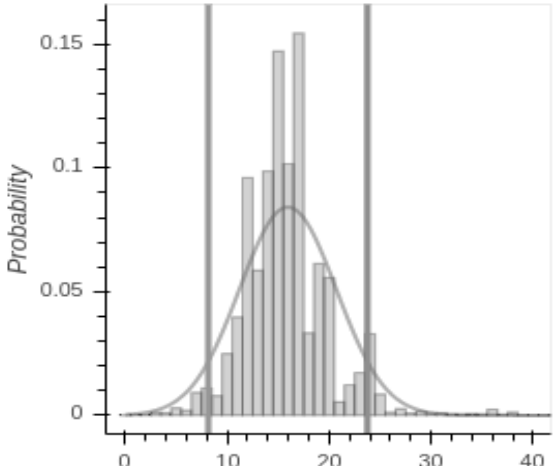
Results

The SI(t+1) prediction accuracy of the proposed NN based prediction method was evaluated by comparing the mean value, the standard deviation, and the 5% and 95% percentile values with the reference data in the interval of values, including the majority (97%) of the data points.

The output of the CDN network prediction in the function of input values showed that the mean value's dependency is closed to linear from the value. The standard deviation also grows proportionally with the . 5% and 95% percentile values show similar behavior to the standard deviation as well.

The accuracy of the CDN based prediction was compared with the currently used stochastic model of the STAR protocol.

1. Table: True/False prediction rate table (STAR vs. CDN network)



1. Figure: Output of the CDN network. The histogram is the raw output, the curve is the fitted normal distribution, the two vertical lines are the 5th and 95th percentiles.

CDN	***True***	0.885279	0.053680
	False	0.015954	0.045087

In Table 1 the 90% confidence interval of the SI(t+1) prediction was compared with the real SI(t+1) value extracted from the treatment records. The True rate in the first row of the table shows the proportion of the cases when the neural network 90% confidence interval includes the real SI(t+1) value. Similarly, the table's first column shows the proportion of the cases when the STAR stochastic model 90% confidence interval includes the real SI(t+1) value.

Discussion

Considering the comparison of the proposed prediction method's statistical parameters and the reference data set, it can be clearly seen that the CDN method met the main criteria. The predicted intervals contain the corresponding SI(t+1) values in more than 90% of the cases. The study was limited to the statistical evaluation of the prediction results on the given data set. Prior to the clinical application of the results, extensive validation will be necessary.

The neural network based method was also compared with the STAR stochastic model currently used in clinical treatment. It can be seen in this table that the total true rate – i.e., the proportion of cases when the 90% confidence interval defined by the given method – of the neural network is almost 4% higher (93.90% vs. 90.12%) than the true rate of the current STAR prediction. In 5.3% of the cases, the classification deep neural network suggests an appropriate confidence interval so that the STAR prediction was not accurate in the given case, and only 1.59% of the cases happen in a reverse way. These numbers suggest that the classification deep neural network is somewhat better in prediction accuracy from the STAR clinical application aspect. However, the quantitative differences are relatively small, so in-silico trials should further investigate the accuracy differences.

Conclusion

A neural network based insulin sensitivity prediction method was presented that can be used in the STAR tight glycaemic control protocol. The suggested method prediction accuracy was the same or better than the currently used stochastic model accuracy. These results are the initial successful step in the proposed methods' validation procedure and will be further validated by in-silico simulation trials.

The presented results proved the applicability of the neural network based method for the patients' state prediction in the model-based clinical

treatment. This method allows more flexible inclusion of further patient parameters into the patient state prediction process, which promises better clinical therapy in the future.

Acknowledgment

Grants supporting the research presented: National Research Development and Innovation Fund, OTKA K116574; TKP2020 BME-Biotechnology FIKP grant of EMMI (BME FIKP-BIO); EU H2020 MSCA-RISE: DCPM (#872488) grant.

References

[1] Naeem A Ali, James M OBrien Jr, Kathleen Dungan, Gary Phillips, Clay B Marsh, Stanley Lemeshow, Alfred F Connors Jr, and Jean-Charles Preiser. Glucose variability and mortality in patients with sepsis. *Critical care medicine*, 36(8):2316, 2008.

[2] Karen C McCowen, Atul Malhotra, and Bruce R Bistrian. Stress-induced hyperglycemia. *Critical care clinics*, 17(1):107–124, 2001.

[3] Benyó, Balázs ; Szlávecz, Ákos ; Homlok, József ; Anane, Yahia ; Kovács, Katalin ; Illyés, Attila ; Chase, J. Geoffrey Személyre szabható inzulin terápia az intenzív ápolásban In: Bari, Ferenc; Rárosi, Ferenc (eds.) Orvosi Informatika 2018. A XXXI. Neumann Kollokvium konferencia-kiadványa Szeged, Hungary : Neumann János Számítógép-tudományi Társaság (NJSZT), (2018) pp. 86-92. , 7 p. Publication:30343176 Admin approved Core Chapter in Book (Conference paper)

[4] Kent W Stewart, Christopher G Pretty, Hamish Tomlinson, Felicity L Thomas, József Homlok, Szabó Némedi Noémi, Attila Illyés, Geoffrey M Shaw, Balázs Benyó, and J Geoffrey Chase. Safety, efficacy and clinical generalization of the STAR protocol: a retrospective analysis. *Annals of intensive care*, 6(1):24, 2016.

[5] J Geoffrey Chase, Aaron J Le Compte, Fatanah Suhaimi, Geoffrey M Shaw, Adrienne Lynn, Jessica Lin, Christopher G Pretty, Normy Razak, Jacquelyn D Parente, Christopher E Hann, et al. Tight glycemic control in critical care–the leading role of insulin sensitivity and patient variability: a review and model-based analysis. *Computer methods and programs in biomedicine*, 102(2):156–171, 2011.

[6] Aaron Le Compte, J Geoffrey Chase, Glynn Russell, Adrienne Lynn, Chris Hann, Geoffrey Shaw, Xing-Wei Wong, Amy Blakemore, and Jessica Lin. Modeling the glucose regulatory system in extreme preterm infants. *Computer methods and programs in biomedicine*, 102(3):253–266, 2011.

[7] Benyó, B. ; Paláncz, B. ; Szlávecz, Á. ; Szabó, B. ; Anane, Y. ; Kovács, K. ; Chase, J. G. *Artificial Intelligence Based Insulin Sensitivity Prediction for Personalized Glycaemic Control in Intensive Care* IFAC PAPERSONLINE , 6 p. (2020) Journal Article/Conference paper in journal (Journal Article)

[8] Vincent Uyttendaele, Jennifer L. Knopp, Shaun Davidson, Thomas Desaive, Balazs Benyo, Geoffrey M. Shaw, and J. Geoffrey Chase. 3D kernel-density stochastic model for more personalized glycaemic control: development and in-silico validation. *BioMedical Engineering OnLine*, 18(1):102, 2019.